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## Summary of the Comparative Effectiveness Review on Off-Label Use of Atypical Antipsychotics

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### **Target Audiences**

This CME activity is designed to meet the educational needs of physicians, psychologists, pharmacists, nurses, and case managers.

### **Learning Objectives**

Based on the findings from AHRQ's comparative effectiveness review of research of off-label use of atypical antipsychotics:

1. Summarize the trends and novel uses of off-label applications of atypical antipsychotics
2. Assess the comparative benefits and harms of off-label applications of atypical antipsychotics on patient subpopulations
3. Discuss the efficacy and comparative effectiveness of atypical antipsychotics for off-label indications

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#### DISCLOSURES

Alicia R. Maher received compensation from PRIME Education, Inc. for work performed in creating this supplement. George Theodore is an employee of PRIME Education, Inc., a medical education company that receives grants and funding for educational programs from various pharmaceutical manufacturers. Theodore analyzed the source document, wrote this summary, and revised this summary with the assistance of Maher.

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#### DISCLOSURE OF OFF-LABEL USE

This report describes uses of atypical antipsychotics (aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone) that are not approved by the U.S. Food and Drug Administration.

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# Summary of the Comparative Effectiveness Review on Off-Label Use of Atypical Antipsychotics

Alicia R. Maher, MD, and George Theodore, PhD

## ABSTRACT

**BACKGROUND:** Conventional and atypical antipsychotic medications are approved by the FDA for treatment of schizophrenia and bipolar disorder. Over many decades, the widespread use of conventional antipsychotics produced various side effects requiring additional medications, such as the atypical antipsychotics. Beginning in 2006, 9 atypical antipsychotic drugs have been approved by the FDA for indications that were previously off-label uses: aripiprazole (as augmentation for major depressive disorder [MDD] and for autism spectrum disorders), asenapine, clozapine, iloperidone, olanzapine (in combination with fluoxetine for MDD and bipolar depression), paliperidone, quetiapine (quetiapine and quetiapine XR [extended release] as monotherapy in bipolar depression and quetiapine XR as augmentation for MDD), risperidone (for autism spectrum disorders), and ziprasidone. In 2006, the Agency for Healthcare Research and Quality (AHRQ) published a systematic review on the comparative effectiveness of off-label uses of atypical antipsychotics. Since that time, numerous studies have been published evaluating these therapies in various new off-label uses; new or increased adverse effects have been observed with off-label uses; new atypical antipsychotics have been approved; and previously off-label uses have been approved for some atypical antipsychotics. Hence, AHRQ published an updated review in September 2011 that summarized the benefits and harms of atypical antipsychotics in the treatment of attention-deficit hyperactivity disorder/attention deficit disorder (ADHD), anxiety, behavioral disturbances of dementia and severe geriatric agitation, depression, eating disorders, insomnia, obsessive-compulsive disorder (OCD), personality disorder, post-traumatic stress disorder (PTSD), substance use and dependence disorders, and Tourette's syndrome. The new report also investigated topics for which data in the previous report were found to be insufficient to make conclusions, including subpopulations (i.e., race/ethnicity, gender) that would benefit most from atypical antipsychotics, appropriate dose, and time needed to see clinical improvement. The 2011 review included the following atypical antipsychotics: aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone; no clinical trials were found for off-label use of the 3 most recently FDA-approved atypical antipsychotics (asenapine, iloperidone, and paliperidone).

**OBJECTIVES:** To (a) familiarize health care professionals with the methods and findings from AHRQ's 2011 Comparative Effectiveness Review (CER) of off-label use of atypical antipsychotics, (b) encourage consideration of the clinical and managed care applications of the review findings, and (c) identify limitations and gaps in the existing research with respect to the benefits and risks of off-label use of atypical antipsychotics.

**SUMMARY:** Antipsychotic medications are FDA approved for the treatment of schizophrenia and bipolar disorder. Conventional antipsychotics have been widely used for decades and spurred the development of the atypical antipsychotics. Atypical antipsychotics were produced and are now being used for patients who may have experienced various side effects while using conventional antipsychotics.

In 2006, an AHRQ study reviewed off-label uses of atypical antipsychotics (excluding clozapine because of its association with potentially fatal bone marrow suppression and the requirement for frequent blood tests for safety monitoring). Findings indicated that the most common off-label uses of these drugs included depression, OCD, PTSD, personality disorders, Tourette's syndrome, autism, and agitation in dementia. The reviewers concluded in 2006 that overall there was not sufficiently high strength of evidence of efficacy for any off-label use of atypical antipsychotics. There was, however, strong evidence for an increased risk of adverse events with off-label use, including significant weight gain and sedation and increased mortality among the elderly.

Since the 2006 review, significant developments occurred in the use of atypical antipsychotics, including FDA approval of the atypical antipsychotics asenapine, iloperidone, and paliperidone and FDA approval of previous off-label uses: (a) quetiapine and quetiapine XR as monotherapy in bipolar depression; (b) quetiapine XR as augmentation therapy for MDD; (c) aripiprazole as augmentation therapy for MDD; (d) olanzapine/fluoxetine combination for MDD; (e) olanzapine/fluoxetine combination for bipolar depression; and (f) risperidone and aripiprazole for autism spectrum disorders. Additional studies have been published for new off-label uses, and there have been reports of new or increased adverse effects for off-label uses.

Further review of previously insufficient information was warranted on subpopulations where treatment modification such as dosing may increase efficacy. The 2006 review did not have sufficient information to make conclusions regarding subpopulations (i.e., race/ethnicity, gender) that would benefit most from atypical antipsychotics, appropriate dosing, and the duration of treatment needed to see clinical improvement.

The updated AHRQ report in 2011 reviewed off-label uses of atypical antipsychotic medications in anxiety, ADHD, behavioral disturbances of dementia and severe geriatric agitation, MDD, eating disorders, insomnia, OCD, PTSD, personality disorders, substance abuse, and Tourette's syndrome; autism was included in the 2006 review but is now reviewed in a separate report of the comparative effectiveness of antipsychotics for on-label uses. The significant findings in the updated review include (a) small but statistically significant benefits for olanzapine, aripiprazole, and risperidone for elderly patients with dementia; (b) quetiapine appears superior to placebo for general anxiety disorder (GAD); (c) risperidone was associated with benefits in the treatment of OCD; and (d) adverse events are common. Atypical antipsychotics were not effective in the treatment of eating disorders or personality disorder. The evidence did not support the use of atypical antipsychotics in the treatment of substance abuse, and data were inconclusive for the use of these medications for insomnia. The number needed to harm (NNH) was calculated for adverse events in elderly patients, including risk of death (NNH=87), stroke (NNH=53 for risperidone), extrapyramidal symptoms (NNH=10 for olanzapine and NNH=20 for risperidone), and urinary symptoms (NNH=16 to 36). Adverse events in nonelderly adults included weight gain (particularly with olanzapine), fatigue, sedation, akathisia (with aripiprazole), and extrapyramidal symptoms.

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Antipsychotic medications are approved by the U.S. Food and Drug Administration (FDA) for the treatment of schizophrenia and bipolar disorder (Table 1). In 2006, the Agency for Healthcare Research and Quality (AHRQ) published a systematic review on the comparative effectiveness of off-label uses of atypical antipsychotics. Beginning in 2006, 9 atypical antipsychotic drugs have been approved by the FDA for indications that were previously off-label uses: aripiprazole (as augmentation for major depressive disorder [MDD] and for autism spectrum disorders), asenapine, clozapine, iloperidone, olanzapine (in combination with fluoxetine for MDD and bipolar depression), paliperidone, quetiapine (quetiapine and quetiapine XR [extended release] as monotherapy in bipolar

**TABLE 1** Currently Approved Atypical Antipsychotics

Drug	Date of Original FDA Approval <sup>a</sup>
Clozapine <sup>b</sup>	September 26, 1989
Risperidone	December 29, 1993
Olanzapine	September 30, 1996
Quetiapine	September 27, 1997
Ziprasidone	February 5, 2001
Aripiprazole	November 15, 2002
Paliperidone <sup>c</sup>	December 19, 2006
Illoperidone <sup>c</sup>	May 6, 2009
Asenapine <sup>c</sup>	August 13, 2009

<sup>a</sup>Derived from FDA information at <http://www.accessdata.fda.gov>.

<sup>b</sup>Excluded from this comparative effectiveness review.

<sup>c</sup>No evidence of off-label use was discovered for these drugs.

FDA = U.S. Food and Drug Administration.

**TABLE 2** Therapeutic Indications of Atypical Antipsychotics Recently Approved by the FDA

Therapy	Approved (On-Label) Use	Date of Approved Use <sup>a</sup>
Aripiprazole	Augmentation for MDD	September 20, 2006
Aripiprazole	Autism spectrum disorders	November 20, 2007
Olanzapine/fluoxetine	Combination for MDD	July 17, 2007
Olanzapine/fluoxetine	Combination for bipolar depression	July 17, 2007
Quetiapine	Monotherapy in bipolar depression	October 23, 2006
Quetiapine ER	Monotherapy in bipolar depression	May 17, 2007
Quetiapine ER	Augmentation for MDD	May 17, 2007
Risperidone	Autism spectrum disorders	October 6, 2006

<sup>a</sup>Derived from FDA information at <http://www.accessdata.fda.gov>

ER = extended release; FDA = U.S. Food and Drug Administration; MDD = major depressive disorder.

depression and quetiapine XR as augmentation for MDD), risperidone (for autism spectrum disorders), and ziprasidone (Table 2).

This supplement summarizes the key findings from the AHRQ 2011 Comparative Effectiveness Review (CER),<sup>1</sup> which describes the efficacy and harms of off-label use of atypical antipsychotics, updated from the 2006 AHRQ CER report.<sup>2</sup> Scientific literature on the utilization, efficacy, adverse effects, dosing, and treatment duration on patient outcomes is reviewed in order to inform prescribing decisions. Applications of the AHRQ findings to practice are discussed to provide clinicians information to support evidence-based care for their patients.

### Off-Label Use of Antipsychotics

**Anxiety.** Each year, approximately 40 million Americans aged 18 years or older suffer from excessive anxiety, defined as irrational dread of common, everyday situations.<sup>3,4</sup> This disabling disorder can be treated with medication (e.g., antidepressants), psychotherapy, or both.<sup>5</sup> Anxiety disorders are characterized by abnormal or pathological fear and anxiety and include acute stress disorder, agoraphobia (with or without a history of panic disorder), generalized anxiety disorder (GAD), and panic disorder (with or without agoraphobia).<sup>5</sup> Although obsessive-compulsive disorder (OCD) and post-traumatic stress disorder (PTSD) are also anxiety disorders, for the purposes of the CER update they were covered separately. Among these disorders, the one most commonly treated with atypical antipsychotics is GAD, which affects 6.8 million American adults. A diagnosis of GAD requires at least 6 months of persistent and excessive anxiety and worry that may lead to insomnia, difficulty concentrating, and social and occupational impairment.<sup>4</sup>

**ADHD.** Attention-deficit hyperactivity disorder (ADHD) and its subtypes are characterized by hyperactivity, inattention, and impulsive behavior.<sup>1</sup> ADHD is the most common disorder

diagnosed in school-age children but may persist into adulthood. Diagnosis requires having 6 or more symptoms persisting for more than 6 months, leading to impairments in 2 settings, such as home and work. Symptoms must be exhibited prior to 7 years of age and must be considered maladaptive.<sup>1,4</sup> Evaluations for ADHD are done in relation to the patient's developmental level, and symptoms must not be attributable to other conditions or pathologies. Psychotherapy, pharmacotherapy, and educational interventions are used alone or in combination to improve outcomes in ADHD.

**Dementia.** Deficits in more than 1 domain of cognitive function (memory, language production and understanding, naming and recognition, skilled motor activity, and planning and executive functioning) define dementia.<sup>1,6</sup> The 2 most common forms of dementia, Alzheimer's and vascular dementia, have distinct causes, although they commonly co-occur. Psychotic symptoms are frequent, and behavioral disturbances often lead to placement in a nursing home. Management of dementia may include behavioral and psychopharmacologic interventions, such as acetylcholinesterase inhibitors or antipsychotics.<sup>6</sup>

**Depression.** Depression is a symptom cluster that may include low mood; inability to experience pleasure; disturbances in sleep and appetite; loss of energy; difficulty concentrating; feelings of guilt, worthlessness, and hopelessness; and suicidal thoughts.<sup>7</sup> Depressive symptoms are seen in a variety of disorders, including unipolar depression, bipolar depression, major depression with or without psychotic features, and depression occurring with psychotic disorders (e.g., schizophrenia or schizoaffective disorder).<sup>8</sup> Current pharmacologic treatment guidelines for major depression are expressed algorithmically. Intolerable side effects or lack of improvement following an adequate trial are potential reasons for treatment failure.<sup>9</sup>

Common pharmacotherapy includes serotonin-enhancing antidepressants, antidepressants with dual reuptake inhibition (serotonin and norepinephrine), and augmenting agents, including the atypical antipsychotics.<sup>1,2</sup> A combination of antidepressant and atypical antipsychotic is often used in cases that include psychotic features.<sup>9,10</sup>

**Eating Disorders.** Eating disorders include anorexia nervosa and bulimia nervosa, the causes of which are poorly understood.<sup>1,8</sup> Eating disorders usually begin in late adolescence or early adulthood and affect men as well as women, although they are more common in women.<sup>11</sup> Medications, nutritional counseling, and psychotherapy are commonly used to treat eating disorders.

**Insomnia.** Insomnia is characterized by persistent difficulty falling asleep and/or difficulty staying asleep.<sup>8</sup> The term “insomnia” was used in the CER update to cover all 4 types of sleep disorders (primary sleep disorders, sleep disorder related to another mental disorder, sleep disorder due to a general medical condition, and substance-induced sleep disorder). Medications, pain, hormonal shifts, and mental and other medical disorders may all cause insomnia,<sup>12</sup> making this a multifaceted disorder. Criteria for a diagnosis of primary insomnia include various types of temporal sleep disturbances that must cause significant distress or functional impairment, must not occur during the course of another mental or medical disorder, and must not be due to the physiological effects of a substance (e.g., alcohol, medication).<sup>1,8</sup>

**Obsessive-Compulsive Disorder.** OCD is characterized by (a) repetitive, intrusive, unwanted thoughts, impulses, or images and (b) compensatory compulsive behaviors that reduce or remove the distress caused by the obsessions.<sup>13</sup> Psychiatric morbidity results from distress and the time devoted to compulsions, as well as compulsion-induced dysfunction. Standard treatments include psychopharmacologic approaches using serotonin reuptake inhibitors, such as fluoxetine, and cognitive-behavioral therapy, which promotes a kind of learning through exposure to the feared or unpleasant stimulus and prevention of the compulsive response.<sup>1,13</sup> Limited response to both treatments is common, and various psychopharmacologic agents, including the atypical antipsychotics, have been tested for their abilities to augment serotonin reuptake inhibitors.

**Post-Traumatic Stress Disorder.** Following exposure to trauma such as war or rape, patients may experience PTSD and manifest debilitating symptoms that may be categorized as re-experiencing, avoidance and numbing, and increased arousal.<sup>14</sup> Patients with PTSD may have symptomatic mood, anxiety, and psychotic effects that may respond to atypical antipsychotics. Cognitive-behavioral and other psychotherapies are also implemented in the treatment of PTSD symptoms.<sup>14</sup>

**Personality Disorders.** The *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV-TR)<sup>8</sup> defines 10 personality disorders. These have in common an onset in adolescence or early adulthood, stability over time, and progression to distress or impairment.<sup>8</sup> Because of the nature of these disorders, they are primarily treated with psychotherapy to facilitate long-term personality change, although medications may play a role in moderating some of the symptomatic manifestations. Schizotypal personality disorder (SPD) and borderline personality disorder (BPD) were the only 2 personality disorders treated with atypicals in clinical trials.<sup>1</sup> Patients with SPD undergo behavioral and perceptual changes that are often similar to mild schizophrenia, which is the rationale for using atypical antipsychotics in this condition. Similarly, atypical antipsychotics have been used in BPD due to the occurrence of psychotic symptoms and mood disturbance.

**Substance Abuse.** The CER update covered substance abuse and dependence on substances including alcohol, cocaine, marijuana, heroin, ecstasy, methamphetamine, and opioids. Caffeine and nicotine dependence were excluded. Substance abuse is a pattern of substance use leading to many adverse results from continual use.<sup>8</sup> Diagnosis of dependence is based upon continual substance use despite significant problems related to the substance.<sup>8</sup>

**Tourette's Syndrome.** Tourette's syndrome is characterized by multiple, rapid, recurrent, stereotyped motor movements and vocal tics. Diagnosis requires that tics occur by 18 years of age, but usually patients experience tics around 6 years of age. Pharmacologic treatments include antipsychotic medications, clonidine, benzodiazepines, and some tricyclic antidepressants.<sup>1</sup>

## Systematic Review Methods

This section summarizes the methods by which the CER was conducted. Complete details about the methods are provided in the full technical report published by AHRQ.<sup>1</sup>

## Key Questions and Comparisons

The investigators attempted to answer the following 5 key clinical questions:

**Key Question 1.** What are the leading off-label uses of atypical antipsychotics in utilization studies? How have trends in utilization changed in recent years, including inpatient versus outpatient use? What new uses are being studied in trials?

**Key Question 2.** What does the evidence show regarding the efficacy and comparative effectiveness of atypical antipsychotics for off-label indications?

**Sub-Key Question 2.** How do atypical antipsychotic medications compare with other drugs, including conventional antipsychotics, for treating off-label indications?



**Key Question 3.** What subset of the population would potentially benefit from off-label uses? Do efficacy, effectiveness, and harms differ by race/ethnicity, gender, and age group? By severity of condition and clinical subtype?

**Key Question 4.** What are the potential adverse effects and/or complications involved with off-label prescribing of atypical antipsychotics? How do they compare within the class and with other drugs used for the conditions?

**Key Question 5.** What are the effective dose and time limit for off-label indications?

### Literature Search and Study Selection

Studies included in the CER update were identified through comprehensive searches of published biomedical literature using the following: PubMed (which includes MEDLINE), EMBASE, PsychINFO, DARE, CINAHL, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, and ClinicalTrials.gov. Searches of these databases were conducted by the reviewers and staff at the Evidence-based Practice Center (EPC) for the period from June 1, 2008, through May 2011 for aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone. The search for off-label use of the newly approved atypicals (iloperidone, paliperidone, and asenapine) included all years available in the electronic databases through May 2011. The EPC also searched for relevant trials in the National Institutes of Health (NIH) Clinical Trials database, the FDA and Health Canada databases, references of included studies, references of relevant reviews, personal files from related topic projects, and unpublished studies requested from pharmaceutical manufacturers. Two investigators reviewed the studies against a screening form that collected data on medication, psychiatric condition, study design, population, sample size, and study duration. Existing systematic reviews; randomized controlled trials; nonrandomized clinical trials; and large observational studies, where appropriate, were included in the review. Studies that did not report any outcomes of efficacy, effectiveness, safety/adverse events, or utilization patterns were excluded. The reviewers did not limit inclusion by study duration. Clinical trials were used to review efficacy outcomes, and observational studies were used when no clinical trials were found for a given condition or drug of interest. All reported side effects and adverse events were abstracted from clinical trials, even if the trial did not report efficacy or effectiveness results. Large observational studies of adverse events were included, as were reports of utilization and prescribing patterns if they discussed use since 1995. The updated review used the National Library of Medicine's Medical Subject Headings (MeSH) key word nomenclature with the same basic search rules used for the original report. New terms and generic names were added for the additional pharmacotherapies covered in the update.

### Evaluations of Study Quality and Rating the Strength of the Body of Evidence

EPC investigators independently assessed the quality of each included study based on the Jadad scale, which scores randomization, blinding, and description of withdrawals and dropouts.<sup>1,15,16</sup> Investigators assessed quality of observational studies using the Newcastle-Ottawa Scale, which evaluates selection, comparability (of cohorts), and outcomes.<sup>1</sup>

Overall study quality was assessed as *good*, *fair*, or *poor* based on the risk for bias. Studies rated as *good* had the least bias, with formal randomized designs and results that were considered valid and devoid of reporting errors. *Fair* studies were susceptible to some bias and had missing information, while *poor* studies had high risk of bias with errors in reporting and design flaws that might have invalidated the results.

At the completion of the review, the EPC investigators graded the strength of evidence for each condition using criteria recommended by the AHRQ *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*.<sup>16</sup> Investigators assessed the strength of evidence by evaluating the number of included studies, strength and quality of study design, consistency of results, directness (i.e., the intervention is linked directly with the most important health or ultimate outcomes), precision, and the magnitude of the effect. The evidence was graded as *high*, *moderate*, *low*, or *insufficient*. *High* strength of evidence indicates high confidence that the evidence reflects the true effect, and further research is unlikely to change confidence in the estimate of the effect. *Moderate* strength of evidence indicates moderate confidence that the evidence reflects the true effect, but further research may change confidence in the estimate of the effect or change the estimate. *Low* strength of evidence indicates low confidence in the reported effect, and further research is expected to change confidence in the estimate of the effect and is likely to change the estimate. A grade of *insufficient* indicated that the evidence was not available or did not permit a conclusion.

### Key Question 1: Utilization of Atypical Antipsychotics

The 2011 CER report made these conclusions for Key Question 1:

- Atypical antipsychotics have been studied as off-label treatment for the following conditions: ADHD, anxiety, behavioral disturbances of dementia in elderly patients, depression, eating disorders, insomnia, OCD, personality disorder, PTSD, substance use disorders, and Tourette's syndrome.
- The most common atypical antipsychotics prescribed for off-label use are risperidone, quetiapine, and olanzapine, and their use for the treatment of elderly patients has increased in long-term care settings.<sup>17-23</sup>
- One recent study found a decrease in overall use of atypical antipsychotics especially among dementia patients following a 2005 regulatory warning from the FDA and



## Summary of the Comparative Effectiveness Review on Off-Label Use of Atypical Antipsychotics

**TABLE 3** Efficacy of Atypical Antipsychotics by Condition and Strength of Evidence

	Aripiprazole	Olanzapine	Quetiapine	Risperidone	Ziprasidone
<b>Anxiety</b>					
Generalized anxiety disorder	○	-	++	-	-
Social phobia	○	+	-	○	○
<b>Attention-deficit hyperactivity disorder</b>					
No co-occurring disorders	○	○	○	+	○
Bipolar children	-	○	○	○	○
Mentally retarded children	○	○	○	+	○
<b>Dementia</b>					
Overall	++	+	+	++	○
Psychosis	+	+-	+-	++	○
Agitation	+	++	+-	++	○
<b>Depression</b>					
MDD augmentation of SSRI/SNRI	++ <sup>a</sup>	+ <sup>a</sup>	++ <sup>a</sup>	++	+
MDD monotherapy	○	-	++	○	○
<b>Eating disorders</b>					
	○	--	-	○	○
<b>Insomnia</b>					
	○	○	-	○	○
<b>Obsessive-compulsive disorder</b>					
Augmentation of SSRI	○	+	--	++	-
Augmentation of citalopram	○	○	+	+	○
<b>Personality disorder</b>					
Borderline	+	+-	+	○	-
Schizotypal	○	○	○	+-	○
<b>Post-traumatic stress disorder</b>					
	○	+-	+	++	○
<b>Substance abuse</b>					
Alcohol	--	-	-	○	○
Cocaine	○	-	○	-	○
Methamphetamine	-	○	○	○	○
Methadone clients	○	○	○	-	○
<b>Tourette's syndrome</b>					
	○	○	○	+	-

Symbol legend: For strength of evidence: ++ = moderate or high evidence of efficacy; + = low or very low evidence of efficacy; +- = mixed results; - = low or very low evidence of efficacy; -- = moderate or high evidence of inefficacy; ○ = no trials.

Source: Maglione M, Ruelaz Maher A, Hu J, et al. Off-label use of atypical antipsychotics: an update. AHRQ comparative effectiveness review no. 43. September 2011.<sup>1</sup>

<sup>a</sup>FDA approved for this indication.

FDA = U.S. Food and Drug Administration; MDD = major depressive disorder; SNRI = serotonin norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

Health Canada describing increased mortality among elderly people with dementia who were taking atypical antipsychotics.<sup>24</sup> Atypical antipsychotic medications are also frequently used for the treatment of PTSD by the U.S. Department of Veterans Affairs (VA) health system.<sup>25,26</sup> Studies in this patient population indicated that quetiapine and risperidone were the atypicals most frequently prescribed off-label at the VA.

- One study of a large psychiatric institution found that quetiapine was often prescribed for a variety of off-label uses; depression and substance abuse were among the most common.<sup>27</sup>
- National trends in the outpatient treatment of children and adolescents over the past decade indicate a sharp increase in the treatment of mental health problems and conditions.<sup>28,29</sup>

- Among children and adolescents, more than 90% of the antipsychotics prescribed were atypical (most commonly risperidone), and they were used off-label.<sup>28,29</sup>
- The reviewers concluded that, overall, use of atypical antipsychotics for various population subgroups has increased over the last decade.

### Key Question 2: Efficacy and Comparative Effectiveness of Atypical Antipsychotics

The reviewers compared their current findings on efficacy with those of the 2006 CER report and updated the findings (Appendix). No trials of off-label use were found for the 3 most recently FDA-approved atypical antipsychotics (asenapine, iloperidone, and paliperidone).<sup>1</sup> There were no head-to-head trials of atypicals for MDD, personality disorders, PTSD, or substance abuse (Table 3).

**TABLE 4** Generalized Anxiety Disorder: Pooled PCTs

Author, Year	Subjects	N	Treatments	Duration	Outcomes
Bandelow et al. 2009 <sup>39</sup>	Aged 18-65 years, diagnosed GAD, HAM-A total score $\geq 20$ with item 1 and 2 scores $\geq 2$ , MADRS total score $\leq 16$ , CGI-S score $\geq 4$ at enrollment and randomization	873	Placebo Quetiapine 50-150 mg per day Quetiapine 50 mg per day Paroxetine 20 mg per day	8 weeks	% responders on HAM-A: Quetiapine vs. placebo—relative risk = 1.36 (95% CI = 1.17-1.59)
Joyce et al. 2008 <sup>40</sup>	Diagnosed GAD	710	Placebo Quetiapine 50 mg per day Quetiapine 150 mg per day	8 weeks	% responders on HAM-A: Quetiapine vs. placebo—relative risk = 1.02 (95% CI = 0.85-1.21)
Merideth et al. 2008 <sup>38</sup>	DSM-IV diagnosis of GAD, HAM-A total score $\geq 20$ with item 1 and item 2 scores $\geq 2$ , CGI-S $\geq 4$ , MADRS $\leq 16$	854	Placebo Escitalopram 10 mg per day Quetiapine 150 mg per day Quetiapine 300 mg per day	8 weeks	% responders on HAM-A: Quetiapine vs. placebo—relative risk = 1.46 (95% CI = 1.21-1.76)

Source: Maglione M, Ruelaz Maher A, Hu J, et al. Off-label use of atypical antipsychotics: an update. AHRQ comparative effectiveness review no. 43. September 2011.<sup>1</sup> CI = confidence interval; CGI-S = clinical global impression-severity; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, 4th ed.; GAD = generalized anxiety disorder; HAM-A = Hamilton Anxiety Scale; mg = milligram; MADRS = Montgomery-Asberg Depression Rating Scale; mg = milligrams; PCT = placebo-controlled trial.

## ADHD

ADHD was not included in the previous report, but the update included 3 placebo-controlled trials (PCTs) and 1 active-control trial, ranging from 4 to 6 weeks, for this condition.<sup>1,2</sup> There were no trials of quetiapine, olanzapine, or ziprasidone for ADHD. Risperidone was superior to placebo in reducing scores on the Children's Aggression Scale-Parent version (CAS-P) in children with no serious co-occurring disorders.<sup>30</sup> All patients receiving risperidone responded (defined as an improvement of 30% over their baseline CAS-P scores) versus only 77% of placebo-treated patients.<sup>31</sup> In another trial of risperidone versus methylphenidate in mentally retarded children with ADHD, there was a greater reduction in SNAP-IV (Swanson, Nolan, and Pelham teacher & parent rating scale) scores with risperidone.<sup>31</sup> Data from 2 trials evaluating aripiprazole (vs. placebo or vs. aripiprazole plus methylphenidate) showed no difference in SNAP-IV scores in children with bipolar disorder or ADHD.<sup>32,33</sup>

## Anxiety

Anxiety disorders were also not included in the previous report.<sup>1,2</sup> The literature search identified 18 relevant trial reports for the treatment of anxiety with atypical antipsychotics, with Jadad scores ranging from 2 to 5 with a mean score of 3.1.<sup>1</sup> The 2011 CER update included 15 PCTs evaluating atypical antipsychotics in the treatment of anxiety.<sup>1</sup> Sample sizes varied widely; follow-up time ranged from same day to 1 year; and most of the PCTs for anxiety reported HAM-A (Hamilton Anxiety Scale) as the primary outcome measure.<sup>1</sup> Trials that did not use the HAM-A evaluated the use of quetiapine and olanzapine for social anxiety disorder. These trials found olanzapine superior to placebo<sup>34</sup> and did not find quetiapine superior to placebo.<sup>1,35,36</sup>

In one previous meta-analysis of quetiapine treatment, monotherapy was significantly superior to placebo for GAD.<sup>37</sup>

Three PCTs of quetiapine monotherapy for GAD were pooled based on their clinical similarities, and a comparison of relative risk of responding on the HAM-A favored quetiapine over placebo (Table 4).<sup>38-40</sup> All 3 trials had a quetiapine 150 milligram (mg) comparison group, and the pooled estimate of the relative risk of responding on the HAM-A in favor of the quetiapine treatment groups was 1.26 (95% confidence interval [CI] = 1.02-1.56).<sup>1,38-40</sup> Another PCT evaluated quetiapine monotherapy as maintenance treatment for GAD and found that it reduced the risk of relapse of anxiety events compared with placebo.<sup>41</sup> A PCT of ziprasidone reported no difference in the HAM-A score at 8 weeks, compared with placebo.<sup>42</sup>

Augmentation studies were separated from studies of monotherapy. A small (N=20) study found that quetiapine augmentation of selective serotonin reuptake inhibitor (SSRI) treatment resulted in 60% responders on the HAM-A versus 30% with placebo augmentation (not statistically significant).<sup>43</sup> A similar study with more participants (N=409) found no statistical difference in HAM-A response rate at 8 weeks. Quetiapine as augmentation of paroxetine for refractory GAD did not provide a significant benefit over placebo augmentation.<sup>44</sup>

There were few head-to-head comparisons, but in a trial of risperidone and paroxetine for panic attacks, significant improvements were reported in the HAM-A for both groups.<sup>45,46</sup> For the treatment of GAD, at 8 weeks, one trial found 50 or 150 mg per day quetiapine as effective as paroxetine 20 mg per day,<sup>43</sup> and another trial found 150 or 300 mg per day quetiapine as effective as 10 mg per day escitalopram.<sup>40</sup>

## Dementia

Although results of previous meta-analyses of atypical antipsychotics in the treatment of behavioral disturbances of dementia in the elderly were mixed, the current review included a new meta-analysis with the previously included trials as well as newer trials.<sup>45-48</sup> However, the reviewers conducted their own

review on 37 trials in patients with dementia that compared aripiprazole, olanzapine, quetiapine, and risperidone with placebo and with another active drug.<sup>1</sup> Of these trials, 18 clinically similar PCTs reporting outcomes at 6-12 weeks were pooled for analysis.<sup>1</sup> The Jadad scores ranged from 0-5 with a mean score of 3.0; hence, the quality of these trials varied widely.<sup>1</sup> Outcomes were divided into 3 categories: total/global scores, psychosis, and agitation. Total global score included many psychiatric symptoms such as delusions, anxiety, and apathy as measured by the Neuropsychiatric Inventory (NPI). Psychosis was measured with a focus primarily on delusions and hallucinations by subscales of the Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD), the Brief Psychiatric Rating Scale (BPRS), and NPI. Agitation was measured by subscales of the BEHAVE-AD, BPRS, NPI, and Cohen-Mansfield Agitation Inventory and included physical aggression, verbal aggression, excitability, oppositional behaviors, and excessive motor ability.<sup>1</sup> A significant difference was observed between atypical antipsychotics (as a class) compared with placebo for all outcomes: total/global scores (standardized mean difference [SMD] 0.17 [95% CI=0.08-0.25]), psychosis (SMD 0.12 [95% CI=0.04-0.19]), and agitation (SMD 0.20 [95% CI=0.12-0.27]). While the minimum clinically important difference is not known, these effect sizes were generally considered "small" in magnitude.<sup>1</sup>

### Depression—MDD

The 2006 CER report found that when atypicals were used as augmentation to SSRIs, they were not more effective than placebo at 8 weeks, but they led to more rapid improvement in some trials (2 to 4 weeks). Although meta-analyses published after 2006 found no statistical difference between specific atypical antipsychotics in increasing response and remission rates, atypicals were found superior to placebo. By 2011, new meta-analyses of trials augmenting SSRIs or serotonin norepinephrine reuptake inhibitors (SNRIs) with atypical antipsychotics showed that several atypicals have efficacy in treatment of depression when used as augmentation. These meta-analyses also showed efficacy for quetiapine monotherapy. In pooled analysis conducted by the reviewers, the relative risk of responding on Hamilton Depression Rating Scale (HAM-D) scores for participants taking quetiapine or risperidone as augmentation was significantly higher than for placebo.

In 3 PCTs reporting the Montgomery-Asberg Depression Rating Scale (MADRS), the relative risk of responding for participants taking aripiprazole was significantly higher than for placebo. In one PCT reporting MADRS, risperidone was statistically superior to placebo. Another PCT that reported MADRS found ziprasidone statistically superior to placebo. The reviewers conducted a meta-analysis of 5 recent trials of quetiapine monotherapy for MDD and found that the relative risk of remitting on the MADRS was statistically superior for

quetiapine compared with placebo. In one trial, quetiapine was superior to lithium with respect to HAM-D and MADRS scores.

### Eating Disorders

Off-label use for the treatment of eating disorders was not included in the 2006 CER. In the 2011 update, 5 trials of olanzapine were found; in 3 pooled studies there was no difference between olanzapine and placebo in body mass index (BMI) increase at 1 or 3 months. One trial of quetiapine also reported no statistical difference in BMI increase at 3 months.

### Insomnia

Off-label use for insomnia was not included in the 2006 CER. Recently, one small trial of quetiapine did not report a statistical difference from placebo in sleep outcomes. Two observational studies of olanzapine and 4 of quetiapine found promising improvements in sleep quality and sleep onset.

### OCD

Meta-analysis in the 2006 CER found that atypicals had a clinically important benefit when used as augmentation to SSRIs. Similar findings were reported in 3 published meta-analyses. The 2011 analysis of PCTs reporting Y-BOCS (Yale-Brown Obsessive Compulsive Scale) outcomes showed significant effects for risperidone as augmentation in treatment of refractory patients. Separate pooling for olanzapine could not be conducted, and the difference in effect was not statistically significant versus placebo. Two new trials after the 2006 CER found quetiapine superior to placebo as augmentation to citalopram. One new trial found quetiapine augmentation of an SSRI superior to augmentation with clomipramine. One head-to-head trial of olanzapine versus risperidone as SSRI augmentation for OCD found no differences. Quetiapine had greater efficacy than ziprasidone in another head-to-head trial.

### Personality Disorders

All trials from the 2006 CER reported efficacy of olanzapine and of aripiprazole for BPD. More recently, PCTs of atypicals for treatment of BPD have had heterogeneous outcomes, and meta-analysis could not be performed.

### PTSD

No trials of aripiprazole or ziprasidone for PTSD were found. The 2006 CER reported that atypicals had beneficial results for combat-related PTSD in 3 PCTs with augmentation for PTSD in male veterans. Three PCTs had mixed results for atypical monotherapy in abused women. These trials were not sufficient to conduct meta-analysis. In a meta-analysis of risperidone and olanzapine studies, the results were not separated by drug. This study found atypicals superior to placebo as measured by change in the Clinician Administered PTSD Scale (CAPS) score. In 2011, 5 clinically similar PCTs were pooled based on

changes in the CAPS score. In 4 trials, risperidone was superior to placebo, and olanzapine was superior to placebo in the other trial. A 3-fold decline in CAPS scores was reported in patients on quetiapine monotherapy compared with patients treated with placebo in another trial. Meta-analysis of risperidone treatment by trial length found that pooled results from at least 12 weeks follow-up were not statistically different from those reported at less than 12 weeks. In another meta-analysis by condition, atypicals showed efficacy in treatment of combat-related PTSD but not PTSD in abused women.

### Substance Abuse

Although off-label use in the treatment of substance abuse was not covered in the 2006 CER report, the updated CER included 2 PCTs of aripiprazole and 1 of quetiapine that reported the percentage of alcohol abusers completely abstinent during the follow-up period. In pooled analysis, the drugs had insignificant efficacy compared with placebo. Two PCTs of olanzapine and 1 of risperidone in cocaine users were pooled, and no difference in efficacy (as measured by change in the Addiction Severity Index) was found versus placebo. Aripiprazole was inefficacious in reducing use of intravenous amphetamine in 1 PCT and inefficacious in reducing craving for methamphetamine in another PCT. In a PCT of methadone clients, no difference was seen between risperidone and placebo in reducing the use of cocaine or heroin. One trial of aripiprazole versus naltrexone in alcohol abusers found no difference in either mean number of days abstinent nor percentage of participants completely abstinent.<sup>1</sup> Augmenting naltrexone with quetiapine produced no difference from placebo augmentation in any alcohol use outcomes. The comparison of risperidone versus pergolide found neither more efficacious than placebo in reducing cocaine use.

### Tourette's Syndrome

The 2006 CER found risperidone superior to placebo in 1 small PCT and at least as efficacious as pimozide or clonidine for 8 to 12 weeks of therapy in 3 other trials. One PCT of ziprasidone showed variable efficacy compared with placebo. No new trials of atypicals have been published since the 2006 CER.

### ■ Key Question 3: Efficacy and Harms with Off-Label Use in Subpopulations and Severity and Subtype of Condition

There were insufficient data to determine which subpopulation would benefit from off-label uses of atypicals.<sup>1</sup> One study of aripiprazole as adjunct therapy in MDD conducted a subgroup analysis by gender and found no statistically significant difference. Few studies stratified results by age, but none stratified by racial or ethnic group. The reviewers' pooled analysis of combat-related PTSD in men found a mean difference in CAPS of 7.95 (95% CI = 1.06-14.84) compared with placebo.<sup>1</sup> Separate publications described the PTSD studies without performing head-to-head comparison of gender effects within a study. The

reviewers were not able to conclude whether any observed differences were due to gender or due to the type of PTSD being treated (combat vs. abuse). Due to the varying measures utilized in determining severity of illness, it was not possible to analyze treatment effects by severity of illness across any other condition in this review. Overall, there was insufficient evidence to make conclusions regarding differences in efficacy between subpopulations.

### ■ Key Question 4: Comparison of Adverse Effects of Off-Label Use of Atypical Antipsychotics Within the Class and Other Drugs

Safety data were assessed based on the type of comparisons involved, which included head-to-head, active, and placebo comparisons (Table 5).

### Weight Gain

Weight gain was evaluated in adults and elderly patients taking atypical antipsychotics. In the large CATIE-AD (Clinical Antipsychotic Trials of Intervention Effectiveness-Alzheimer's Disease) trial, elderly placebo patients averaged a monthly weight loss of 0.9 lbs., while patients treated with the various atypical antipsychotics averaged monthly weight gains; 1 pound with olanzapine, 0.7 pounds with quetiapine, or 0.4 pounds with risperidone.<sup>49</sup> Elderly patients with a BMI less than 25 at the start of the cohort study experienced weight gain more commonly while on olanzapine than risperidone or conventional antipsychotics. Meta-analysis of placebo comparisons revealed that weight gain was more common in elderly patients treated with olanzapine and risperidone compared with placebo.<sup>1</sup> The review included a single trial evaluating the effects on weight gain among adults aged 18 to 64 years and again found weight gain to be more common among olanzapine patients than ziprasidone patients. In this age group, olanzapine was more commonly associated with weight gain than was conventional treatment with antipsychotics or treatment with mood stabilizers.<sup>1</sup> Overall, weight gain was more common for aripiprazole-treated patients when compared with patients treated with conventional antipsychotics. The reviewers' meta-analysis found that weight gain was less common in patients taking placebo compared with aripiprazole, olanzapine, quetiapine, and risperidone.<sup>1</sup> As in the 2006 report, high-strength evidence across multiple trials showed greater weight gain with olanzapine compared with placebo, conventional antipsychotics, or other atypical antipsychotics.<sup>1,2</sup> Although the strength of evidence was stronger in the update, the reviewers commented that the evidence was not as robust as in the 2006 report. In nonelderly adults, the association of olanzapine, risperidone, quetiapine, and aripiprazole with weight gain was statistically significant versus placebo. An association was found for weight gain with ziprasidone therapy, but these data were not statistically significant.

## Summary of the Comparative Effectiveness Review on Off-Label Use of Atypical Antipsychotics

**TABLE 5** Safety of Atypical Antipsychotics for Off-Label Use<sup>a</sup>

Adverse Event	Head-to-Head Comparisons	Active Comparisons	Placebo Comparisons
<b>Weight gain—</b> elderly patients	In 1 large trial (CATIE-AD), patients who were treated with olanzapine, quetiapine, or risperidone averaged a monthly gain of 1.0, 0.7, and 0.4 lbs, respectively, compared with a monthly weight loss of 0.9 lbs for placebo patients.	More common in patients taking olanzapine than risperidone or conventional antipsychotics, particularly if BMI was less than 25 at baseline, according to a large cohort study.	More common in patients taking olanzapine and risperidone than placebo according to our meta-analysis.
<b>Weight gain—</b> adults aged 18 to 64 years	More common in olanzapine patients than ziprasidone patients in 1 trial.	More common among patients taking olanzapine than patients taking conventional antipsychotics in 3 trials.  More common in patients taking aripiprazole than patients taking conventional antipsychotics in 1 trial.  More common among patients taking olanzapine than patients taking mood stabilizers in 2 trials.	More common in patients taking aripiprazole, olanzapine, quetiapine, and risperidone than placebo according to our meta-analysis.
<b>Weight gain—</b> children and adolescents	No head-to-head studies.	No difference between clonidine and risperidone in 1 trial.	More common in patients taking risperidone in 2 PCTs. No difference in 1 small PCT of ziprasidone.
<b>Mortality—</b> elderly patients	No difference between olanzapine and risperidone according to a meta-analysis of 6 trials of olanzapine published in 2006.	6 large cohort studies compared mortality in elderly patients taking atypical and conventional antipsychotics. 4 of these studies found a significantly higher rate of death with conventional antipsychotics, while 2 found no statistical difference in mortality between the drug classes.	Difference in risk for death was small but statistically significant for atypicals, according to a 2006 meta-analysis, which remains the best available estimate. Sensitivity analyses found no difference between drugs in the class.  Patients taking atypicals had higher odds of mortality than those taking no antipsychotics in the 2 cohort studies that made that comparison.  There are no trials or large observational studies of ziprasidone in this population; therefore, we cannot make conclusions regarding safety here.
<b>Endocrine/ diabetes—</b> elderly patients	No evidence reported.	No evidence reported.	No difference in endocrine events in risperidone patients in 1 PCT.  Regarding diabetes, risk was elevated but not statistically significant in one industry-sponsored cohort study of olanzapine patients.
<b>Endocrine/ diabetes—</b> adults aged 18 to 64 years	Diabetes more common in patients taking olanzapine than patients taking risperidone in 1 trial.	No evidence reported.	Endocrine events more common in patients taking quetiapine, risperidone, and ziprasidone in 1 PCT each. More common in olanzapine in 2 pooled PCTs.  Diabetes more common in patients taking quetiapine in 6 pooled PCTs; however, the pooled odds ratio was elevated at 1.47 but not statistically significant. More common in olanzapine patients in 1 PCT; the odds ratio of 5.14 was not statistically significant, with very wide confidence intervals (0.6 to 244).  Lower odds of diabetes in risperidone patients in one large observational study.
<b>CVA—</b> elderly patients	No evidence reported.	Hospitalization for CVA was increased in the first week after initiation of conventional antipsychotics, but not for initiation of atypicals in a large cohort study.	More common in risperidone patients than placebo according to 4 PCTs pooled by the manufacturer. In our new meta-analysis of PCTs, risperidone was the only drug associated with an increase.  More common in olanzapine than placebo according to 5 PCTs pooled by the manufacturer.
<b>EPS—</b> elderly patients	More common in patients taking aripiprazole and risperidone than patients taking quetiapine in 1 large trial (CATIE-AD).	No evidence reported.	More common in patients taking risperidone, according to our meta-analysis. Quetiapine and aripiprazole were not associated with an increase.  More common in olanzapine in 1 PCT.

## Summary of the Comparative Effectiveness Review on Off-Label Use of Atypical Antipsychotics

**TABLE 5** Safety of Atypical Antipsychotics for Off-Label Use<sup>a</sup> (continued)

Adverse Event	Head-to-Head Comparisons	Active Comparisons	Placebo Comparisons
<b>EPS—</b> adults aged 18 to 64 years	No evidence reported.	Less likely in patients taking quetiapine than mood stabilizers in 1 small trial.  Less likely in patients taking olanzapine or aripiprazole than patients taking conventional antipsychotics in 1 trial each.	More common in patients taking aripiprazole, quetiapine, and ziprasidone than placebo according to our meta-analysis.
<b>Sedation—</b> elderly patients	More common in elderly patients taking olanzapine or quetiapine than risperidone according to our analysis, but not quite statistically significant.	No difference in 1 trial of olanzapine vs. benzodiazepines.  No difference in 3 trials of olanzapine and 3 of risperidone vs. conventional antipsychotics.	More common in patients taking aripiprazole, olanzapine, quetiapine, and risperidone than placebo according to our meta-analysis.
<b>Sedation—</b> children and adolescents	No head-to-head trials.	No difference in 1 small trial of clonidine vs. risperidone. More patients on haloperidol than risperidone reported sleep problems in one trial.	Less common in aripiprazole patients than placebo patients in 1 PCT. No difference from placebo in 1 small PCT of ziprasidone.
<b>Sedation—</b> adults aged 18 to 64 years	More common in patients taking quetiapine than risperidone in 2 trials.  No difference in 1 trial of risperidone vs. olanzapine.	Olanzapine patients had higher odds than mood stabilizer patients in 2 trials.  More common in olanzapine and quetiapine patients than SSRI patients in 3 and 2 trials, respectively.  Olanzapine patients had lower odds than patients taking conventional antipsychotics in our pooled analysis of 3 trials.	More common in patients taking aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone than placebo in our meta-analysis.

Source: Maglione M, Ruelaz Maher A, Hu J, et al. Off-label use of atypical antipsychotics: an update. AHRQ comparative effectiveness review no. 43. September 2011.<sup>1</sup>

<sup>a</sup>Some of the text included in this table is identical to the source text.

BMI=body mass index; CATIE-AD=Clinical Antipsychotic Trials of Intervention Effectiveness-Alzheimer's Disease; CVA=cerebrovascular accident; EPS=extrapyramidal symptoms; lbs=pounds; PCT=placebo-controlled trial; SSRI=selective serotonin reuptake inhibitor.

### Metabolic Symptoms

The occurrence of endocrine events including diabetes among adults (aged 18-64 years) and the elderly was a new focus included in the 2011 CER.<sup>1</sup> Among elderly patients, no difference in risk was found comparing placebo with risperidone treatment, and an observed elevated risk of diabetes for olanzapine treatment was not significantly associated with treatment but rather depended on elevated glucose levels at baseline. In adults aged 18 to 64 years, olanzapine was associated with a greater risk of diabetes when compared with risperidone, and lower odds of diabetes were reported in risperidone patients compared with placebo in 1 large observational study.<sup>50-53</sup> Six pooled PCTs found diabetes to be more common among quetiapine-treated patients, but the elevated pooled odds ratio of 1.47 (95% CI=0.71-3.28) for these patients was not statistically significant.<sup>1</sup> The updated report noted an emerging safety signal of an increase in urinary tract symptoms with atypical antipsychotics.<sup>1</sup> This increase was noted in older adults with behavioral disturbances of dementia treated with atypical antipsychotics as compared with placebo-treated patients.

### Extrapyramidal Symptoms

Extrapyramidal symptoms (EPS), including acute dystonic reactions, pseudoparkinsonism, and akathisia, were examined

in the recent review in adults and elderly patients treated with atypical antipsychotics. The large CATIE-AD trial found symptoms to be more common in elderly patients taking aripiprazole and risperidone than in those taking quetiapine.<sup>50</sup> In the CATIE-AD trial, EPS were more common with olanzapine and risperidone than quetiapine.<sup>49</sup> This trial concluded that all 3 of these therapies were associated with cognitive decline in patients with dementia who were treated with these drugs. Meta-analysis conducted by the reviewers revealed that EPS were more common in elderly patients on risperidone compared with placebo, but quetiapine and aripiprazole were not associated with increased EPS.<sup>1</sup> The association of olanzapine and risperidone with an increase in extrapyramidal signs or symptoms versus placebo had moderate strength of evidence. In a group of another 7 studies that were evaluated via pooled analysis in this review, quetiapine was again associated with EPS.<sup>1</sup>

### Mortality

Data from meta-analyses were found to be of high strength for the association of atypical antipsychotics with an increased risk of death among the elderly with agitation and dementia.<sup>1</sup> For risperidone, this outcome may be related to an increased risk of stroke. A new finding in this update is the stronger evidence that conventional antipsychotics also increase the

risk of death in similar patients, perhaps to the same or greater degree than atypical antipsychotics. This finding is qualified by a moderate strength of evidence, relying on data mostly from observational studies of high quality.

With respect to mortality among the elderly, no difference was found in the head-to-head comparison for olanzapine versus risperidone. Results from active comparisons of atypical and conventional antipsychotics were split, with 4 studies reporting a significantly higher rate of death for conventional antipsychotics and 2 studies reporting no statistical difference in mortality.<sup>1</sup> Such findings were difficult to assess in the review. The 2006 meta-analysis, which found a small but statistically significant difference in risk for death for atypical antipsychotics, remains the best available estimate of their effect on mortality.<sup>2</sup>

### Sedation

Sedation is another adverse effect commonly associated with atypical antipsychotics. The reviewers analyzed data on sedation for elderly patients taking olanzapine and quetiapine. Sedation was more common in these patients compared with risperidone, but this difference was not statistically significant.<sup>1</sup> In this elderly population, there was no difference for olanzapine versus benzodiazepines or compared with conventional antipsychotics. Among the elderly, no difference in the risk of sedation was seen for risperidone therapy versus conventional antipsychotics. Meta-analysis of PCTs also found that aripiprazole, olanzapine, quetiapine, and risperidone were each associated with both sedation and fatigue in patients with dementia. Similarly, increases in sedation and fatigue were found for ziprasidone versus placebo in adults aged 18 to 64 years.<sup>1</sup> In adults in that age group, sedation was more common with quetiapine versus risperidone, and no differences were found in a comparison of olanzapine with risperidone. Olanzapine-treated patients did have higher odds of experiencing sedation symptoms than those taking mood stabilizers, but the odds were lower for olanzapine patients when compared with those taking conventional antipsychotics in a pooled analysis of the data.<sup>1</sup> Sedation was more common in patients taking SSRIs compared with olanzapine and quetiapine therapy. Among children and adolescents, no difference in sedation was observed in a small trial of clonidine versus risperidone, but more patients reported sleep problems on haloperidol compared with risperidone. Compared with placebo, sedation was less common in aripiprazole-treated patients, and no difference was observed with ziprasidone treatment.

### Cerebrovascular Accidents

The updated summary included data on cerebrovascular accidents (CVAs) among elderly patients. Hospitalization for CVA increased in the first week after the start of therapy with conventional antipsychotics but not with atypicals.<sup>1</sup> CVAs were more common in elderly risperidone patients than in placebo-treated individuals. This finding was based on data from 4

pooled studies and from a meta-analysis of PCTs. More CVAs were also observed for olanzapine compared with placebo.<sup>1</sup> No studies of any drug or condition reported on CVA in younger adults.

### Key Question 5: Dosage and Treatment Duration for Off-Label Indications

Conclusions could not be drawn by the reviewers as to the minimum dose needed to achieve efficacy, since very few studies compared doses of atypical antipsychotic medications. Most patients enrolled in trials took a wide range of doses, complicating the establishment of conclusions by the investigators. Meta-analysis was conducted using the percentage of remitters and responders according to the MADRS as an outcome and found no statistical difference for 150 mg quetiapine daily augmentation versus augmentation with 300 mg for inadequate responders to SSRI with MDD.<sup>1</sup> Trial data for duration of treatment and outcomes seemed the same for PTSD, eating disorders, and BPD, regardless of the follow-up time used.

### Study Limitations and Directions for Future Research

Unidentified, unpublished, or excluded studies might have reported different results from those included in this review. The meta-analysis, particularly for behavioral disturbances of dementia, includes broad heterogeneity across patients and treatment circumstances. Furthermore, the reviewers noted the possibility of publication bias in the studies. The studies used variable definitions and measures of agitation, which complicates the clinical interpretation and application of these findings.<sup>1</sup> Comparisons of atypical antipsychotics with nonpharmacological therapy were not made. Very few studies were funded with federal grants, and most were privately funded. However, the government-sponsored CATIE-AD study reported results consistent with the industry-sponsored studies, increasing confidence in the conclusions regarding atypical antipsychotic medications for elderly patients with dementia.<sup>49</sup> Future research should include more federally funded studies, head-to-head comparisons between the various atypical antipsychotic medications, and standardized definitions of both treatments and response. More trials examining different doses of other atypicals for MDD would help guide clinicians in treating this population. In addition, more dosage trials for treating such conditions as OCD, PTSD, and GAD would allow for pooling and comparisons of results.<sup>1</sup> Lastly, some studies on the use of medications for insomnia will surely augment the strength of evidence available for this topic, since only 1 small trial was previously found.

### Conclusions

The 2011 AHRQ-sponsored review addressed many uses for atypical antipsychotics in conditions that were not covered in the previous report. The 2011 CER found high strength of



evidence of small but statistically significant benefits for the use of aripiprazole, olanzapine, and risperidone in elderly patients for management of behavioral symptoms associated with dementia. There was moderate strength of evidence that aripiprazole, quetiapine, and risperidone have efficacy as augmentation to SSRIs/SNRIs for MDD and that quetiapine had efficacy as monotherapy for MDD. Olanzapine did not have efficacy as monotherapy for MDD, and that finding was supported by moderate strength of evidence.

Moderate strength of evidence supported efficacy for risperidone treatment improving OCD symptoms when used as an adjunct to SSRI in treatment-refractory patients and in reducing combat-related PTSD symptoms when used as an adjunct to primary medication. Additional moderate strength of evidence was found for quetiapine efficacy as treatment for GAD. The lack of efficacy for olanzapine in increasing BMI among patients with eating disorders was also supported by moderate strength of evidence. Finally, moderate strength of evidence was collected demonstrating that aripiprazole was not efficacious in treating alcohol abuse/dependence.

The rest of the strength of evidence was low or very low. Low strength of evidence showed that olanzapine and ziprasidone may have efficacy as augmentation to SSRIs/SNRIs for MDD. In addition, low strength of evidence showed that olanzapine may have efficacy in improving OCD symptoms when used as an adjunct to SSRI in treatment-refractory patients and that quetiapine may be efficacious as augmentation to citalopram in patients with OCD. Furthermore, quetiapine was more efficacious than ziprasidone and clomipramine for the treatment of OCD. For the treatment of BPD, there was low strength of evidence from 2 trials that found aripiprazole was efficacious. Risperidone had mixed results when used to treat SPD in 2 small trials, and the strength of evidence was low. Regarding Tourette's syndrome, treatment with risperidone was at least as efficacious as pimozide or clonidine.

The reviewers evaluated different types of ADHD and found

low strength of evidence that for ADHD without co-occurring disorders, risperidone therapy may be efficacious in the treatment of children. Low strength of evidence was found for the lack of efficacy from aripiprazole in reducing ADHD symptoms in children with bipolar disorder. Low strength of evidence supported the superiority of risperidone treatment over methylphenidate in treating ADHD symptoms in mentally retarded children.

Quetiapine was not efficacious (low strength of evidence) in increasing BMI among patients with eating disorders. The lack of efficacy found for quetiapine treatment for alcohol abuse/dependence was also supported with low strength of evidence. For treatment of cocaine abuse/dependence, low strength of evidence showed that olanzapine was not efficacious. For other types of substance abuse, low strength of evidence showed that aripiprazole was inefficacious in treating methamphetamine abuse/dependence and that risperidone is an inefficacious adjunct to methadone maintenance.

The remaining evidence evaluated in the 2011 review was considered to be of very low strength. Very low strength of evidence supported the finding that risperidone may be efficacious as augmentation to citalopram in OCD. Additional data of very low strength of evidence for the treatment of BPD showed that olanzapine had mixed results in 7 trials; quetiapine was efficacious in 1 trial; and ziprasidone was not efficacious in 1 trial. In addition, evidence of very low strength was found for the inefficacy of quetiapine in treating insomnia.

The updated 2011 review contained additional data from recently published scientific literature on the comparative benefits and adverse effects of the off-label use of atypical antipsychotics. The findings demonstrated that off-label use of antipsychotics improved symptoms for various conditions, such as agitation among elderly patients with dementia. In this condition, the lack of effective options has led to wide use of atypical antipsychotics. Evidence is still needed for ways to balance the prevention of symptoms through the use of atypical antipsychotics with the risk of serious adverse effects, such as stroke or death among elderly patients.

**Commentary: Managed Care Perspective on Comparative Effectiveness Research on Off-Label Uses of Atypical Antipsychotics**

**Sleep: At What Cost?**

Our nation is in a battle for sleep. More than one-third of Americans report having problems sleeping, and a recent national consumer survey on sleep found that a significant portion of Americans are bringing more and more technology into the bedroom, with activities such as texting in the bedroom in the hour prior to sleep associated with poorer self-assessed sleep quality.<sup>54</sup> Over the past several decades, the pursuit of effective drug therapy by both patients and providers has been vigorous, with nonpharmacologic treatments including cognitive behavioral therapy and improvement in sleep hygiene often taking a secondary role.

Clinicians might be amazed to learn that in the 2011 AHRQ Comparative Effectiveness Review (CER) of off-label uses of atypical antipsychotics reviewers found just 1 study meeting stringent evidence-based inclusion and exclusion criteria that evaluated the safety and effectiveness of an atypical antipsychotic (quetiapine) for the treatment of insomnia. In that 13-patient trial, there was not a statistically significant difference, compared with the use of placebo, in sleep outcomes. While the evidence—limited as it is—is not supportive of the use of atypicals for sleep, clinicians who are utilizing them in clinical practice for this off-label use may argue for “real-world effectiveness.” But, given the risks identified in the review, particularly those of rapid weight gain (present even with low doses), akathisia, and extrapyramidal symptoms, it is hard to justify a prescribing practice that is not supported by evidence of benefit but that is supported by evidence of harm. For improving sleep problems, moving the smart phone, texting, laptops, and tablet computers out of the bedroom and going back to the basics with sleep hygiene certainly represent a less risky initial approach to such a common problem.

**A Tricky Balance: Weighing the Risks and Benefits of Treatment of Agitated Patients with Dementia with Atypical Antipsychotics**

Pharmacists in a variety of inpatient and ambulatory settings are frequently called on by prescribers and caregivers to assist with management of agitation in older adults with dementia. Often, agitation and inability to manage behavioral problems associated with dementia drive a need for transition from either home to assisted living facility or from assisted living facility into a more supervised setting. *Safe and effective* pharmacotherapy for agitated patients with dementia is thus a frequent request to both prescribers and pharmacists from caregivers who are experiencing extreme caregiving stress. Unfortunately, it is the lack of the medications’

ability—in this case atypical antipsychotics—to meet both of these criteria that often (and should always) result in significant family and prescriber discussion regarding the risks and benefits of therapy with atypical antipsychotics.

The careful assessment in the 2011 AHRQ CER of the off-label use of atypical agents for the treatment of agitation in dementia revealed the intricacies of this drug class, as there was significant variation in effect among the atypicals that have been studied, with significant variation as well in the quality of the studies with various atypicals. Compared with the data available in 2006, there has been a strengthening of the evidence to support a small magnitude of effectiveness in the treatment of agitation in dementia for aripiprazole, olanzapine, and risperidone overall when compared with placebo. Specifically for patients with dementia and psychosis, evidence supports benefit over placebo with the use of risperidone, but not with aripiprazole.

With evidence of benefit, while small in magnitude, it is then important to weigh that benefit with the risk of harm. The black box that was applied in 2005 to atypical antipsychotics warning of an increased risk of death in these patients certainly gives clinicians pause when carefully evaluating a patient for treatment. The CER further states that the number needed to harm for increased risk of stroke with risperidone is 56, although both risperidone and olanzapine were significantly more likely to result in a negative outcome than aripiprazole or quetiapine.<sup>55</sup> In addition to this risk, there was an increased risk of weight gain (olanzapine and risperidone); anticholinergic effects (olanzapine); sedation and fatigue (aripiprazole, olanzapine, quetiapine, risperidone); extrapyramidal symptoms (olanzapine and risperidone); and urinary tract symptoms (risperidone, quetiapine, olanzapine). Finally, of significant concern is the association of the use of olanzapine, quetiapine, and risperidone with an increased cognitive decline—the very thing that we are attempting to avoid in these patients.

In summary, use of atypical antipsychotics in agitated patients with dementia is multifactorial, with individual patient characteristics and behavioral consequences shifting the balance of risk and benefit. Furthermore, the selection of a particular agent and the objective documentation of benefit in the trials conducted with atypical antipsychotics may affect the use of these therapies. For each patient, an individual assessment and documentation of risks and benefits of therapy is necessary to making the most appropriate decision for the individual.

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## Summary of the Comparative Effectiveness Review on Off-Label Use of Atypical Antipsychotics

### APPENDIX Efficacy of Atypical Antipsychotics for Off-Label Use<sup>a</sup>

Usage	Strength of Evidence	2006 Findings	2011 Findings	2011 Conclusions
<b>Dementia</b>	High	<p>A published meta-analysis of 15 PCTs found small but statistically significant effects favoring treatment with risperidone and aripiprazole.</p> <p>There were effects that favored treatment with olanzapine for the BPRS and the NPI, but these differences were not statistically significant.</p> <p>Three studies of quetiapine were considered too clinically dissimilar to pool and results for the individual studies showed, with one exception, trends favoring treatment with quetiapine that did not reach conventional levels of statistical significance.</p>	<p>Overall—In our meta-analysis of PCTs, aripiprazole, olanzapine, and risperidone were superior to placebo as treatment of behavioral symptoms as measured by total scores on BEHAVE-D, BPRS, and NPI. Effect sizes were generally considered to be “small” in magnitude.</p> <p>Psychosis—In our meta-analysis risperidone was superior to placebo, as measured by the psychosis subscales of the BEHAVE-AD, BPRS, and NPI. Results for aripiprazole did not meet conventional levels of statistical significance.</p> <p>Agitation—In our meta-analysis, aripiprazole, olanzapine, and risperidone were superior to placebo, as measured by the agitation subscales of the BEHAVE-AD, BPRS, NPI, and CMAI.</p> <p>3 head-to-head trials compared atypicals; none were found to be superior.</p>	Aripiprazole, olanzapine, and risperidone have efficacy as treatment for behavioral symptoms of dementia.
<b>Depression—MDD: augmentation of SSRI/SNRI</b>	Moderate— risperidone, aripiprazole, quetiapine  Low— olanzapine, ziprasidone	<p>3 trials assessed the combination of olanzapine and fluoxetine; 1 trial each assessed augmentation of various SSRIs with risperidone, ziprasidone, and quetiapine; and 1 study assessed adding risperidone vs. olanzapine to SSRI.</p> <p>The combination of olanzapine and fluoxetine was no better than fluoxetine alone in improvement of depressive symptoms at 8 weeks, but 3 trials reported more rapid improvement in depressive symptoms (at 2-4 weeks) with combination therapy using olanzapine or quetiapine.</p> <p>1 trial that directly compared augmentation therapy between olanzapine and risperidone reported no differences in outcome.</p>	<p>We conducted a meta-analysis using “response” to treatment and remission as outcome. Pooling trials that reported the HAM-D as outcome, the relative risk of responding for participants taking quetiapine or risperidone was significantly higher than for placebo. Olanzapine had only 2 trials, so pooling was not performed; the trials reported olanzapine superior to placebo. Other trials reported MADRS scores; the relative risk of responding for participants taking aripiprazole was significantly higher than those taking placebo. Risperidone and ziprasidone were included in 2 and 1 trial, respectively; these reported the drug superior to placebo.</p> <p>1 trial compared ziprasidone at differing levels augmenting sertraline to sertraline alone. This trial found a greater improvement in CGI-S and MADRS scores augmenting with ziprasidone at 160 mg than either augmentation with ziprasidone at 80 mg or sertraline alone. However, there was no significant difference in HAM-D-17, CGI-I or HAM-A scores.</p>	Aripiprazole, quetiapine, and risperidone have efficacy as augmentation to SSRIs/SNRIs for MDD. Olanzapine and ziprasidone may also have efficacy.
<b>Depression—MDD: Monotherapy</b>	Moderate	3 olanzapine studies (above) also assessed its efficacy as monotherapy. Olanzapine alone was no better than placebo in improving symptoms at 6 or 12 weeks. Outcomes were too heterogeneous to allow pooling.	In our meta-analysis of 5 PCTs, quetiapine was superior according to relative risk of both responding and remitted as measured by MADRS.	Olanzapine does not have efficacy as monotherapy for MDD. Quetiapine has efficacy as monotherapy for MDD.
<b>Obsessive-compulsive disorder—augmentation of SSRI</b>	Moderate— risperidone  Low— olanzapine	12 trials used risperidone, olanzapine, or quetiapine as augmentation therapy in patients who were resistant to treatment with SSRI. Nine trials were sufficiently similar clinically to pool. Atypical antipsychotics had a clinically important benefit (measured by the Y-BOCS) when used as augmentation therapy. Relative risk of “responding” significant for augmentation with quetiapine and risperidone. There were too few studies of olanzapine augmentation to permit separate pooling of this drug.	<p>Our updated meta-analysis found risperidone superior to placebo, as measured by changes in the Y-BOCS. There were too few studies (2) to permit separate pooling for olanzapine; both trials reported olanzapine superior to placebo.</p> <p>1 new head-to-head trial found no difference in effect between olanzapine and risperidone as SSRI augmentation. 1 new head-to-head trial found quetiapine more effective than ziprasidone as SSRI augmentation.</p> <p>1 new trial compared quetiapine to clomipramine as SSRI augmentation. Quetiapine produced a significant reduction in Y-BOCS score, while clomipramine did not.</p>	<p>Risperidone has efficacy in improving OCD symptoms when used as an adjunct to SSRI in treatment refractory patients. Olanzapine may also have efficacy.</p> <p>Quetiapine is more efficacious than ziprasidone and clomipramine for this purpose.</p>

## Summary of the Comparative Effectiveness Review on Off-Label Use of Atypical Antipsychotics

### APPENDIX Efficacy of Atypical Antipsychotics for Off-Label Use<sup>a</sup> (continued)

Usage	Strength of Evidence	2006 Findings	2011 Findings	2011 Conclusions
<b>Obsessive-compulsive disorder—</b> augmentation of citalopram	Low—quetiapine Very low—risperidone	1 trial of risperidone reported no differences between groups in achieving a response to therapy, but patients maintained on risperidone had a significantly longer period of time to relapse compared with placebo (102 days vs. 85 days).	Two new trials found quetiapine superior to placebo as augmentation for citalopram, according to Y-BOCS and CGI-I scores.	Quetiapine and risperidone may be efficacious as augmentation to citalopram in OCD patients.
<b>Post-traumatic stress disorder</b>	Moderate—risperidone Olanzapine—low Quetiapine—very low	4 trials of risperidone and 2 trials of olanzapine, each of at least 6 weeks duration, treated patients with PTSD. 3 trials enrolled men with combat-related PTSD; these showed a benefit in sleep quality, depression, anxiety, and overall symptoms when risperidone or olanzapine was used to augment therapy with antidepressants or other psychotropic medication. 3 trials of olanzapine or risperidone as monotherapy for abused women with PTSD were inconclusive regarding efficacy.	3 new trials of risperidone were found, allowing us to conduct a meta-analysis using the CAPS as outcome. Risperidone was superior to placebo. There were too few olanzapine studies (2) to pool; 1 reported olanzapine superior to placebo, while 1 did not.  A new trial found a 3-fold decline in CAPS scores in patients treated with quetiapine monotherapy compared with placebo. Exact scores were not reported.  We also conducted a meta-analysis by condition; atypicals were efficacious for combat-related PTSD but not PTSD in abused women.	Risperidone is efficacious in reducing combat-related PTSD symptoms when used as an adjunct to primary medication.
<b>Personality disorders—</b> borderline	Low—aripiprazole Very low—quetiapine, olanzapine	3 trials provide evidence that olanzapine is superior to placebo and may be superior to fluoxetine. The benefit of adding olanzapine to dialectical therapy in 1 trial was small. Aripiprazole was superior to placebo in 1 small trial.	One new trial found aripiprazole superior to placebo in improving SCL-90, HAM-D, and HAM-A scores at 8 months and less self-injury at 18 months. One new trial of ziprasidone found no significant difference in CGI-BPD, depressive, anxiety, psychotic or impulsive symptoms compared with placebo at 12 weeks. 2 new trials of olanzapine found no difference from placebo in any outcomes, while another new trial of olanzapine found greater change in ZAN-BPD scores at 12 weeks, compared with placebo. 1 new trial found quetiapine superior to placebo on BPRS, PANSS scales. Due to heterogeneity of outcomes, we could not perform a meta-analysis.	Olanzapine had mixed results in 7 trials; aripiprazole was found efficacious in 2 trials; quetiapine was found efficacious in 1 trial; and ziprasidone was found not efficacious in 1 trial.
<b>Personality disorders—</b> schizotypal	Low	Risperidone was superior to placebo in one small trial.	One new small trial of risperidone found no difference from placebo on a cognitive assessment battery.	Risperidone had mixed results when treating schizotypal personality disorder in 2 small trials.
<b>Tourette's syndrome</b>	Low	Risperidone was superior to placebo in 1 small trial, and it was at least as effective as pimozide or clonidine for 8 to 12 weeks of therapy in the 3 other trials. 1 trial of ziprasidone showed variable efficacy vs. placebo.	No additional trials.	Same as 2006: Risperidone is at least as efficacious as pimozide or clonidine for Tourette's syndrome.
<b>Anxiety</b>	Moderate	Not covered.	Three PCTs of quetiapine as monotherapy for GAD could be pooled; relative risk of responding on HAM-A favored the quetiapine group.  1 head-to-head trial showed no difference between risperidone and paroxetine on HAM-A score improvement.  One trial each found quetiapine equally effective as paroxetine and escitalopram.	Quetiapine has efficacy as treatment for GAD.
<b>Attention-deficit hyperactivity disorder—</b> no co-occurring disorders	Low	Not covered	1 trial showed risperidone superior to placebo in reducing scores on the CAS-P version.	Risperidone may be efficacious in treating children with ADHD with no serious co-occurring disorders.

## Summary of the Comparative Effectiveness Review on Off-Label Use of Atypical Antipsychotics

### APPENDIX Efficacy of Atypical Antipsychotics for Off-Label Use<sup>a</sup> (continued)

Usage	Strength of Evidence	2006 Findings	2011 Findings	2011 Conclusions
Attention-deficit hyperactivity disorder—mentally retarded children	Low	Not covered	1 trial showed risperidone led to greater reduction in SNAP-IV scores than methylphenidate.	Risperidone may be superior to methylphenidate in treating ADHD symptoms in mentally retarded children.
Attention-deficit hyperactivity disorder—children with bipolar disorder	Low	Not covered	2 trials of aripiprazole showed no effect on SNAP-IV scores than placebo.	Aripiprazole is ineffective in reducing ADHD symptoms in children with bipolar disorder.
Eating disorders	Moderate—olanzapine Low—quetiapine	Not covered	5 trials of olanzapine were found; 3 reporting BMI could be pooled. There was no difference in change in BMI at either 1 or 3 months compared with placebo.  1 trial of quetiapine reported no statistical difference from placebo in BMI increase at 3 months.	Olanzapine and quetiapine have no efficacy in increasing body mass in eating disorder patients.
Insomnia	Very low	Not covered	1 small trial (N=13) of quetiapine; sleep outcomes were not statistically different from placebo.	Quetiapine may be ineffective in treating insomnia.
Substance abuse—alcohol	Moderate—aripiprazole Low—quetiapine	Not covered	2 trials of aripiprazole and 1 of quetiapine reported percentage of patients completely abstinent during follow-up. In our pooled analysis, the effect vs. placebo was insignificant.	Aripiprazole is ineffective in treating alcohol abuse/dependence. Quetiapine may also be ineffective.
Substance abuse—cocaine	Low	Not covered	2 trials of olanzapine and 1 of risperidone reported there was no difference in efficacy vs. placebo as measured by the ASI.	Olanzapine is ineffective in treating cocaine abuse/dependence. Risperidone may also be ineffective.
Substance abuse—methamphetamine	Low	Not covered	1 trial found aripiprazole ineffective in reducing use of intravenous amphetamine, as measured by urinalysis. Another trial found aripiprazole ineffective in reducing craving for methamphetamine.	Aripiprazole is ineffective in treating methamphetamine abuse/dependence.
Substance abuse—methadone clients	Low	Not covered	1 trial of methadone clients found no difference between risperidone and placebo in reduction of cocaine or heroin use.	Risperidone is an ineffective adjunct to methadone maintenance.

Source: Table B in: Maglione M, Ruelaz Maher A, Hu J, et al. Off-label use of atypical antipsychotics: an update. AHRQ comparative effectiveness review no. 43. September 2011.<sup>1</sup>

<sup>a</sup>Some of the text included in this table is identical to the source text.

ADHD=attention-deficit hyperactivity disorder; ASI=Addiction Severity Index; BEHAVE-AD=Behavioral Pathology in Alzheimer's Disease Rating Scale; BMI=body mass index; BPRS=Brief Psychiatric Rating Scale; CAPS=Clinician Administered PTSD Scale; CAS-P=Children's Aggression Scale-Parent version; CGI-BPD=clinical global impression scale for borderline personality disorder; CGI-I=clinical global impression improvement; CGI-S=clinical global impression-severity; CMAI=Cohen-Mansfield Agitation Inventory; GAD=generalized anxiety disorder; HAM-A=Hamilton Anxiety Scale; HAM-D=Hamilton Depression Scale; MADRS=Montgomery-Asberg Depression Rating Scale; MDD=major depressive disorder; mg=milligram; NPI=Neuropsychiatric Inventory; OCD=obsessive-compulsive disorder; PANSS=Positive and Negative Syndrome Scale; PCT=placebo-controlled trial; PTSD=post-traumatic stress disorder; SCL-90=Symptom Checklist 90; SNAP-IV=Swanson, Nolan, and Pelham teacher & parent rating scale; SNRI=serotonin norepinephrine reuptake inhibitor; SSRI=selective serotonin reuptake inhibitor; Y-BOCS=Yale-Brown Obsessive Compulsive Scale; ZAN-BPD=Zanarini rating scale for borderline personality disorder.





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